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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,295	RIEDEL ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *See Attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are presented for examination.

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 60/446,695, filed February 11, 2003, and 60/503,317, filed September 16, 2003. Acknowledgement is also made of Applicant's claim for priority under 35 U.S.C. 119(a-d) to German Patent Application Nos. 10301371.7, filed January 16, 2003, and 10335027.6, filed July 31, 2003. Applicant's Information Disclosure Statements (IDS) filed February 23, 2004 (two pages), March 26, 2004 (one page) and August 16, 2004 (two pages) have each been received and entered into the application. As reflected by the attached, completed copies of form PTO/SB/08A (five pages total), the Examiner has considered the cited references.

Applicant's Claim for Priority under 35 U.S.C. 119(a-d) and 119(e)

Applicant's claim for the benefit of a foreign-filed application (German Patent Application Nos. 10301371.7 and 10335027.6) under 35 U.S.C. 119(a-d) and Applicant's claim for the benefit of a provisional application (U.S. Provisional Patent Application Nos. 60/446,695 and 60/503,317) under 35 U.S.C. 119(e) is acknowledged. Applicant is reminded that the later-filed application must be an application for patent for an invention that has been disclosed in the prior parent applications. The disclosure of the invention in the earlier application(s) and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Receipt of the certified copies of German Patent Application Nos. 10301371.7, filed January 16, 2003, and 10335027.6, filed July 31, 2003, submitted under 35 U.S.C. 119(a-d), have each been placed of record in the file.

It has been determined that German Patent Application No. 10301371.7, filed January 16, 2003, contains sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter. In light of this fact, the effective filing date of present claims 1-18 has been determined to be January 16, 2003.

Objection to the Specification

It is noted that Applicant has incorporated by reference numerous foreign patents and publications such as, for example, WO 00/43370 (page 21, line 25), EP 0502314 (page 21, line 24), EP 0247633 (page 22, line 23) and the publications listed at page 2 of the specification. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication, is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by a statement executed by the Applicant, or a practitioner representing the Applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Please see 37 C.F.R. 1.57(f). Applicant is required to amend any improper incorporation by reference of essential subject matter, as the above-cited citations may not reflect all of the places at which improper incorporation by reference occurs in the present specification.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4 and 6-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes or hypertensive insulin resistance, does not reasonably provide enablement for the prevention of these conditions or the treatment or prevention of cardiovascular, cardiopulmonary or renal diseases in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the

claims and the state of the prior art in the assessment of undue experimentation. For the purposes of consideration under 35 U.S.C. 112, first paragraph, the Examiner has focused on the particular condition of prediabetes, of which metabolic syndrome is considered to be exemplary, as recited in present claim 4. However, the reasons stated here concerning the burden of enabling the prevention of the prediabetic condition of metabolic syndrome apply also to myriad of other conditions encompassed by the present claims, but for the obvious difference in the type of disorder.

The present rejection is also made under the guidance of the MPEP at §2164.01(c), which states, "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)." Thus, the instant rejection made under 35 U.S.C. 112, first paragraph, is proper as it is applied to present claims 14-18 because the claims are drawn to a composition for the prevention or treatment of cardiovascular, cardiopulmonary or renal diseases.

The present rejection is deemed proper based on the reasoning set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or

use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

Applicant's attention is also directed towards the MPEP at §2164.01(a), which states:

"While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP §2164.01(a) (a.k.a. the "Wands Factors" as delineated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons and evidence that lead the Examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." (emphasis added)

The presently claimed invention in its broadest embodiment is directed towards a method for the prevention or treatment of a cardiovascular, cardiopulmonary or renal disease or condition in a mammal, comprising the administration of telmisartan in combination with atorvastatin. The claims are further directed towards the specific treatment or prevention of hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes or hypertensive insulin resistance and pharmaceutical composition(s) comprising telmisartan and atorvastatin for the treatment or prevention of the same, optionally in combination with a diuretic compound.

Applicant is reminded that the state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also

related to the need for working examples in the specification. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date [*Chiron Corp. v. Genentech Inc.*, 363 F.3d 247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004)]. See MPEP §2164.05(b).

Also, it is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to make and use the *entire scope* of the claimed invention without undue experimentation.

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prediabetic condition of metabolic syndrome, for example, could be effectively prevented by administration of the claimed active agents. Based on the state of the art, as discussed below, the artisan would have only accepted that such a condition could be treated or the incidence of such a condition could be reduced, rather than that it could actually be prevented from ever occurring.

The term "prevent" in the present claims is considered to be comparable to the word "prophylaxis", and both circumscribe methods of absolute success. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by

administering the presently claimed combination of active agents, the incidence of metabolic syndrome would be 0% and there would be a reasonable guarantee that metabolic syndrome would never develop. Such a situation is sufficiently unusual that data would need to be shown in order to establish that metabolic syndrome could be kept from ever occurring through the administration of the claimed active agents. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as metabolic syndrome, the specification, which lacks an objective showing that such a disease could be prevented, is viewed as lacking an enabling disclosure of the same.

Here, the objective truth of the statement in claim 4, for example, that a prediabetic condition, of which metabolic syndrome is considered exemplary, may be prevented, is doubted because the art expressly recognizes the complex nature and poor understanding of this syndrome and the predisposing factors that characterize this condition.

In this regard, Grundy ("Metabolic Complications of Obesity", Endocrine, 2000) is cited. Applicant's attention is drawn particularly to the abstract, which states, "The rising prevalence of obesity is accompanied by an increasing number of patients with the metabolic complications of obesity. The major complications come under the heading of the metabolic syndrome. This syndrome is characterized by plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state. The clinical consequences of the metabolic syndrome are coronary heart disease and stroke, type 2 diabetes and its complications, fatty liver, cholesterol gallstones, and possible some forms of cancer. At the heart of the metabolic syndrome is insulin resistance...Obesity is the predominant factor leading to insulin resistance, although other factors play a role. The mechanistic link between insulin resistance

and the metabolic syndrome is complex. The relationship is modulated by yet other factors, such as physical activity, body fat distribution, hormones, and a person's genetic polymorphic architecture. A better understanding of the molecular basis of this relationship is needed...In addition, understanding at the clinical level will lead to improved management of these complications."

Given that the art expressly acknowledges that the condition of metabolic syndrome and insulin resistance, the primary condition that characterizes metabolic syndrome and results in impaired glucose utilization, as being complex, the skilled artisan would have recognized that the state of the art with regard to metabolic syndrome is not well defined, and is, therefore, unpredictable, such that one of ordinary skill in the art would not accept on its face Applicant's statement that metabolic syndrome could be prevented because the pathophysiology of such a condition is not particularly well characterized. In light of such, the artisan would have required sufficient direction as to how the administration of the presently claimed combination of active agents could actually prevent the development of metabolic syndrome such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected give that absolute prevention is an outcome not reasonably expected by one of ordinary skill in the art and, to the artisan, the concept of a single agent, or even a combination of agents, that is effective in preventing the development of metabolic syndrome would have been unique and, thus, met with a great deal of skepticism.

Furthermore, given the breadth of conditions characterizing metabolic syndrome (i.e., plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state), prevention or prophylaxis against metabolic syndrome

would necessarily involve preventing each one or more of the conditions known to be associated with such a syndrome. Such a situation would require the skilled artisan to determine whether the active agents of the present claims are effective in preventing any one or more of these conditions and such a process would amount to undue experimentation, given the breadth and disparate nature of each of these conditions and the poor clinical understanding of metabolic syndrome in general.

Furthermore, it is noted that one skilled in the relevant art could not practice the entire scope of the presently claimed subject matter in light of Applicant's disclosure without undue experimentation because the artisan would not accept on its face that the use of the pharmaceutical combination of telmisartan and atorvastatin would have efficacy in treating or preventing *any* known cardiovascular disease, *any* known cardiopulmonary disease or *any* known renal disease. In other words, the disclosure as originally filed does not provide sufficient enabling direction commensurate in scope with what is presently claimed such that the skilled artisan would be obviated of the burden of undue experimentation in order to practice the entire scope of the claimed subject matter.

Applicant has provided adequate disclosure teaching the manner and process of using the presently claimed combination of agents for the particular treatment of hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance. However, such disclosure is not sufficient to support a claim to the prevention of such diseases, nor is such a finding reasonably suggestive of extrapolating the activity of the combination of telmisartan and atorvastatin to retain the same level of efficacy in the treatment of any known

cardiovascular, cardiopulmonary or renal disorder. Applicant has failed to establish on the record that the activity of a combination pharmaceutical comprising telmisartan and atorvastatin in treating the specific disorders presently claimed would have been predictive of the same or substantially similar efficacy in treating or preventing any cardiovascular, cardiopulmonary or renal disorder known in the art.

It is noted that the specification lacks an objective showing of evidence or sound scientific reasoning that would reasonably correlate the efficacy of telmisartan and atorvastatin in treating hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance to be an adequate projection of the same or substantially similar efficacy in treating any other cardiovascular, cardiopulmonary or renal disease known in the art. In addition, Applicant has failed to address the breadth and disparate nature of the diseases encompassed by the broad and generic terms "cardiovascular", "cardiopulmonary" or "renal" or the considerable differences in etiology and pathophysiological manifestations. In light of the fact that Applicant has only provided enabling disclosure for the treatment of hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance, a person having ordinary skill in the art would have been highly skeptical to extrapolate the efficacy shown by telmisartan/atorvastatin in treating such conditions to all cardiovascular, cardiopulmonary or renal diseases known in the art, particularly in the absence of any scientific basis for such an extrapolation. While it is acknowledged that Applicants for patent are not required to reduce the invention to practice in every single embodiment that is

claimed, sufficiently persuasive and soundly scientific reasoning must be provided as to why one of ordinary skill in the art would have considered Applicant's disclosure to be reasonably representative of the larger and highly varied genus of cardiovascular, cardiopulmonary or renal disorders in general.

Applicant has merely disclosed that the administration of the presently claimed combination of telmisartan and atorvastatin to a mammal may prevent or treat hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes or hypertensive insulin resistance, or any cardiovascular, cardiopulmonary or renal disease, in general. However, for the reasons already set forth above, it is clear that Applicant has failed to provide any persuasive basis for extrapolating the use of telmisartan and atorvastatin for the treatment of hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance to the larger and highly variable genus of cardiovascular, cardiopulmonary or renal disorders as whole. As a result, the skilled artisan would have had no alternative recourse but undue experimentation to determine what cardiovascular, cardiopulmonary or renal disease other than those expressly claimed would have been effectively treated, or in the extreme case, prevented, using the claimed combination of agents or even whether such was even an objective that could be achieved.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of preventing or treating cardiovascular, cardiopulmonary or renal diseases in general, of which metabolic syndrome is

considered exemplary, there is no apparent data to support the contention that the use of the claim specified active composition could actually prevent the presently claimed conditions (i.e., hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance) by simply administering, by any method, an amount of the claimed active composition comprising telmisartan and atorvastatin, since the present specification fails to enable one of ordinary skill in the art to practice the presently claimed invention insofar as it reads on the prevention of hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes or hypertensive insulin resistance or the prevention or treatment of any cardiovascular, cardiopulmonary or renal disease known in the art.

In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that prevention or treatment of all cardiovascular disorders, all cardiopulmonary disorders or all renal disorders, or the prevention of the specific conditions of hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes or hypertensive insulin resistance, of which metabolic syndrome is considered exemplary, could actually be achieved. In order to actually achieve prevention or treatment of all such conditions, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. §112, first paragraph. Absent such disclosure by Applicant and in light of the disparate nature of each of the cardiovascular, cardiopulmonary or renal

diseases known in the art, the skilled artisan would have been skeptical to extrapolate the enabling disclosure of the present specification regarding the treatment of hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance using telmisartan and atorvastatin to the prevention of these diseases or, more broadly, the prevention or treatment of any cardiovascular, cardiopulmonary or renal disease known in the art.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-7 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by De Gasparo et al. (WO 01/76573; 2001) in light of Robl et al. (U.S. Patent Application Publication No. 2002/0013334; January 31, 2002), cited to show a fact.

In accordance with the MPEP at §2131.01, it is proper to rely upon another reference for a rejection under 35 U.S.C. 102, provided that the reference is relied upon solely to define the meaning of a term used in the primary reference.

De Gasparo et al. teaches a pharmaceutical composition (page 1, line 16; see present claims 14-18) comprising an AT_1-receptor antagonist (page 1, line 27; see present claims 1 and

14-18), or an AT_1-receptor antagonist in combination with a diuretic (page 1, line 27; see present claims 17-18), or pharmaceutically acceptable salts thereof (page 1, line 28; see present claim 1), further in combination with an HMG-CoA reductase inhibitor (page 1, line 29; see present claims 1 and 14-18), and a carrier (page 2, line 1; see present claims 14-18), used for the treatment of hyperlipidemia (page 1, line 8; see present claim 2), atherosclerosis (page 1, line 8; see present claim 2), insulin resistance (page 1, line 9; see present claims 5-6), syndrome X (page 1, line 9; see present claim 5), type 2 diabetes mellitus (page 1, line 9; see present claim 4), renal failure (page 1, lines 9-10; see present claim 1), and all of these diseases of conditions associated with or without hypertension (page 1, lines 12-13; see present claims 2 and 5-6), in a warm-blood animal, including man (page 2, line 4; see present claims 1 and 7), wherein the therapeutically effective amount of AT_1-receptor antagonist given orally (given as a dosage of valsartan, which De Gasparo et al. expressly states is representative of the class of AT_1-receptor antagonists) is 20-320 mg (page 12, lines 12-19; see present claims 14-15) and the dose of HMG-CoA reductase inhibitor given orally is 5-120 mg (page 12, lines 20-23; see present claims 14-15). De Gasparo et al. expressly discloses telmisartan as the AT_1-receptor antagonist (page 3, line 22; see present claims 1-6 and 14-16), atorvastatin as the HMG-CoA reductase inhibitor (page 5, lines 9-11; see present claims 1-6, 14-16) and hydrochlorothiazide and chlorothalidone as diuretic agents (page 4, lines 8-10; see present claims 17-18).

Robl et al. is relied upon to shown that Syndrome X is known to encompass prediabetic insulin resistance syndrome (see paragraph [0107] at page 4). Thus, it is clear that the teaching of "syndrome X" by De Gasparo et al. is synonymous with prediabetes as required by Applicant's present claim 4.

While De Gasparo et al. does not expressly teach an amount of telmisartan from 20-200 mg, the reference does teach an amount of telmisartan ranging from 20-320 mg. Regarding the presently claimed amount of atorvastatin, it is noted that De Gasparo et al. also does not expressly teach an amount of atorvastatin from 2.5-40 mg. However, the reference does teach an amount of atorvastatin ranging from 5-120 mg. Thus, De Gasparo et al. anticipates the entire presently claimed range of telmisartan and anticipates the presently claimed range of atorvastatin insofar as it reads upon an amount of 5-40 mg. See MPEP §2131.03 for a discussion of the anticipation of ranges.

In addition, it is noted that De Gasparo et al. does not expressly teach a weight ratio of atorvastatin to telmisartan. However, such a ratio was calculated by comparing the amount of atorvastatin (5-120 mg) to telmisartan (20-320 mg) as taught by the reference. Insofar as De Gasparo et al. teaches atorvastatin in an amount of 5-120 mg and telmisartan in an amount of 20-320 mg, the reference anticipates the weight ratio of atorvastatin to telmisartan of 1:4 and 1:2.6 as encompassed by present claim 16.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Gasparo et al. (WO 01/76573; 2001) in light of Robl et al. (U.S. Patent Application Publication No. 2002/001334; January 31, 2002), cited to show a fact, in view of Cecil's Textbook of Medicine (2000), Harlan et al. (U.S. Patent Application Publication No. 2001/0006656; July 2001) and Bohm et al. (WO 02/15892; February 2002).

De Gasparo et al. teaches a pharmaceutical composition (page 1, line 16; see present claims 14-18) comprising an AT_1-receptor antagonist (page 1, line 27; see present claims 1 and 14-18), or an AT_1-receptor antagonist in combination with a diuretic (page 1, line 27; see present claims 17-18), or pharmaceutically acceptable salts thereof (page 1, line 28; see present claim 1), further in combination with an HMG-CoA reductase inhibitor (page 1, line 29; see present claims 1 and 14-18), and a carrier (page 2, line 1; see present claims 14-18), used for the treatment of hyperlipidemia (page 1, line 8; see present claim 2), atherosclerosis (page 1, line 8; see present claim 2), insulin resistance (page 1, line 9; see present claims 5-6), syndrome X (page 1, line 9; see present claim 5), type 2 diabetes mellitus (page 1, line 9; see present claim 4), renal failure (page 1, lines 9-10; see present claim 1), and all of these diseases of conditions associated

with or without hypertension (page 1, lines 12-13; see present claims 2 and 5-6), in a warm-blood animal, including man (page 2, line 4; see present claims 1 and 7), wherein the therapeutically effective amount of AT_1-receptor antagonist given orally (given as a dosage of valsartan, which De Gasparo et al. expressly states is representative of the class of AT_1-receptor antagonists) is 20-320 mg (page 12, lines 12-19; see present claims 14-15) and the dose of HMG-CoA reductase inhibitor given orally is 5-120 mg (page 12, lines 20-23; see present claims 14-15). De Gasparo et al. expressly discloses telmisartan as the AT_1-receptor antagonist (page 3, line 22; see present claims 1-6 and 14-16), atorvastatin as the HMG-CoA reductase inhibitor (page 5, lines 9-11; see present claims 1-6, 14-16) and hydrochlorothiazide and chlorothalidone as diuretic agents (page 4, lines 8-10; see present claims 17-18).

Robl et al. is relied upon to shown that Syndrome X is known to encompass prediabetic insulin resistance syndrome (see paragraph [0107] at page 4), which is synonymous with prediabetes as required by Applicant's present claim 4.

The differences between the De Gasparo et al. reference and the presently claimed subject matter lies in that the reference fails to teach:

(i) that the human has the blood parameters of fasting blood sugar, triglycerides, HDL cholesterol or blood pressure as defined in present claims 8-11;

(ii) the use of telmisartan and atorvastatin for the treatment of asthma, bronchitis or interstitial lung disease as recited in present claim 3; or

(iii) the particularly claimed dosage amounts of atorvastatin, telmisartan or diuretic (i.e., hydrochlorothiazide or chlorothalidone) or weight ratio of atorvastatin to telmisartan as defined in present claims 12-13, 15-16 and 18.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) De Gasparo et al. expressly teaches hosts suffering from the presently claimed conditions (i.e., hypertension combined with hyperlipidemia or atherosclerosis, type 2 diabetes mellitus, prediabtes, metabolic syndrome, insulin resistance or hypertensive insulin resistance), but is silent as to the glucose, triglyceride or HDL cholesterol levels or blood pressure of the hosts contemplated by the reference. However, Cecil's Textbook of Medicine (2000) provides teachings of the standard, commonly accepted laboratory normal ranges for (1) normal serum glucose of 74-106 mg/dL, (2) normal serum triglyceride levels of <250 mg/dL; (3) normal HDL levels of >29 mg/dL for males and >35 mg/dL for females and (4) normal systolic blood pressure of <130 mmHg and normal diastolic blood pressure of <85 mmHg (see Cecil's Textbook of Medicine, p.258 and 2299-2304). It would logically follow that the diabetic host of De Gasparo et al. would show elevated serum glucose outside of the normal range (i.e., greater than 110 mg/dL), the hyperlipidemic host would show elevated serum triglyceride levels on the outer limits of or outside the normal range (i.e., greater than 150 mg/dL) and low HDL cholesterol levels (i.e., <40 mg/dL for females and <50 mg/dL for males) and the hypertensive host would show elevated systolic and diastolic blood pressure (i.e., >130 mmHg systolic and >80 mmHg diastolic). While it is acknowledged that the reference standard ranges expressly taught by Cecil's are not exactly identical to those presently claimed, it must be noted that such serum levels of glucose, triglycerides, HDL cholesterol and blood pressure will vary by individual and,

thus, what is considered "normal" or "abnormal" will also vary such that a proper comparison to determine whether a particular laboratory value is normal or abnormal must be made to baseline, values for each patient. Regardless of the minor differences between Cecil's and the present claims, the presently claimed limitations on the diabetic, hyperlipidemic or hypertensive host by claiming particular serum levels of glucose, triglycerides, HDL cholesterol or blood pressure are not considered to impart patentable distinction to the present claims over what would have been logically determined from the teachings of De Gasparo et al. in light of the knowledge generally available to one of ordinary skill in the art at the time of the invention.

(ii) Harlan et al. (U.S. Patent Application Publication No. 2001/0006656; July 2001) provides teachings of the use of an HMG-CoA reductase inhibitor, such as atorvastatin, for the treatment of inflammatory lung diseases, such as asthma, chronic bronchitis and interstitial lung disease (see paragraphs [0022] and [0025-0026] at page 2). Although Harlan et al. is silent as to the concomitant use of an angiotensin antagonist, such as telmisartan, for the treatment of the same, Bohm et al. (WO 02/15892; February 2002) teaches that diseases such as bronchitis, asthma and interstitial lung disease were known to be associated with an increase of AT1 receptors in the subepithelial area and, thus, were amenable to treatment using a composition comprising an AT1 antagonist, such as telmisartan (see page 7, paragraphs 6-7 and page 10, second paragraph).

While De Gasparo et al. is silent as to the particular treatment of asthma, bronchitis or interstitial lung disease, the teachings of Harlan et al. and Bohm et al. raise the reasonable expectation of success that an AT1 antagonist, such as telmisartan, and an HMG-CoA reductase inhibitor, such as atorvastatin, would demonstrate efficacy in the treatment of asthma, bronchitis

or interstitial lung disease when combined, since each was known to be used separately in the art for the same indication(s). Motivation to administer both compounds flows logically from the efficacy of each compound in treating asthma, bronchitis or interstitial lung disease. One having ordinary skill in the art would have been motivated to administer atorvastatin and telmisartan together for the treatment of the same because each compound has been previously administered for these identical therapeutic endpoints and would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. Please reference *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

(iii) The determination of the optimum amounts or weight ratio(s) of atorvastatin and telmisartan to treat the presently claimed diseases (i.e., hypertension combined with hyperlipidemia or atherosclerosis, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance) with the presently claimed active agents would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the amounts or ratios that would have actually been employed would have varied widely and, in the

absence of evidence to the contrary, the currently claimed specific amounts or weight ratio(s) are not seen to be inconsistent with those that would have been determined by the skilled artisan.

Applicant's attention is further drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

I Claims 1-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-35 of U.S. Patent Application No. 10/757,015,

in view of Harlan et al. (U.S. Patent Application Publication No. 2001/0006656; 2001).

This is a provisional double patenting rejection since the conflicting claims of this application have not yet been patented.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims is either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the present application and those of the copending patent application are not considered patentably distinct from each other because the copending claims render the present claims obvious.

In particular, it is noted that the copending claims clearly provide for the treatment of a cardiovascular, cardiopulmonary, or renal disease in a mammal, particularly hypertension combined with hyperlipidemia or atherosclerosis, asthma, bronchitis, interstitial lung disease, diabetes mellitus, prediabetes, metabolic syndrome, insulin resistance or hypertensive insulin resistance in a mammalian host comprising the administration of telmisartan with simvastatin. While the present claims are drawn to the same therapeutic objectives, the present claims recite the administration of telmisartan with atorvastatin. However, the use of atorvastatin instead of simvastatin would have been *prima facie* obvious to one of ordinary skill in the art since atorvastatin was known in the art to have the same inhibitory effect on HMG-CoA reductase as simvastatin (see Harlan et al., paragraph [0025] at page 2) and would have been reasonably expected to exert the same or substantially similar efficacy as simvastatin.

Furthermore, the copending claims are also drawn to a pharmaceutical composition

comprising telmisartan, simvastatin, a carrier and, optionally, a diuretic, which is identical to the composition of the present claims, but for the use of atorvastatin instead of simvastatin. As previously stated, atorvastatin was known in the art to have the same inhibitory effect on HMG-CoA reductase as simvastatin and would have been reasonably expected to exert the same or substantially similar efficacy as simvastatin.

Lastly, while the dosage amounts or concentrations of the active agents to be administered or contained in the composition are not identical between the present claims and the copending claims, it is noted that the determination of the optimum dosage regimen or amounts would have been well within the purview of the skilled artisan and would have been made in accordance with a variety of factors, including, but not limited to, the age, sex, weight, diet, and medical condition of the patient, toxicological considerations and the severity of the disease.

Accordingly, rejection of claims 1-18 of the present application is deemed proper over claims 1-35 of U.S. Patent Application No. 10/757,015 as claiming obvious and unpatentable variants thereof.

II Claims 1, 4-5, 7-11 and 14-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10, 12-15 and 18 of U.S. Patent Application No. 10/899,784.

This is a provisional double patenting rejection since the conflicting claims of this application have not yet been patented.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the

reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the present application and those of the copending patent application are not considered patentably distinct from each other because the present claims render the copending claims obvious.

In particular, it is noted that the present claims clearly provide for the treatment of a patient with diabetes mellitus, prediabetes, metabolic syndrome or insulin resistance using telmisartan in combination with atorvastatin. While the copending claims are drawn to the same therapeutic objectives using an angiotensin II antagonist compound alone, it is noted that the present claims recite the species of telmisartan, while the copending claim are drawn to the genus of angiotensin II antagonists. As taught by the MPEP at §2131.02, a species will always anticipate a claim to a genus. Thus, the species of telmisartan used for the treatment of diabetes mellitus, prediabetes, metabolic syndrome or insulin resistance anticipates the larger genus of angiotensin II antagonists as a whole. Furthermore, there is no reason to doubt that the telmisartan compound of the present claims does not also possess the same binding properties as recited in copending claims 12-13, absent factual evidence to the contrary.

While it is noted that the copending claims are drawn to slightly different blood parameters than those of the present claims, it is submitted that because the host of the present claims and that of the copending claims are identical (i.e., diabetic or prediabetic host, host with metabolic syndrome or insulin resistance, etc.), the recitation of particular serum levels of glucose, triglycerides, HDL cholesterol, or blood pressure are not seen to patentably distinguish the copending claims from the present claims because it is generally known in the art that such

parameters vary by individual and, thus, what may be considered "normal" or "abnormal" for such a person will also vary accordingly. Thus, the parameters of the copending claims are not seen to be inconsistent with those of the present claims or what would have been generally accepted by the skilled artisan to be normal threshold limits.

Accordingly, rejection of claims 1, 4-5, 7-11 and 14-16 of the present application is deemed proper over claims 1-10, 12-15 and 18 of U.S. Patent Application No. 10/899,784 as claiming obvious and unpatentable variants thereof.

III Claims 1-2, 4-7 and 12-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of U.S. Patent Application No. 11/300,947 in view of Drug Facts and Comparisons (1996).

This is a provisional double patenting rejection since the conflicting claims of this application have not yet been patented.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the present application and those of the copending patent application are not considered patentably distinct from each other because the present claims render the copending claims obvious.

In particular, it is noted that the present claims clearly provide for a pharmaceutical composition comprising telmisartan and the diuretic hydrochlorothiazide, while is claimed in the

copending application. While the amounts of each of the active agents differs between the present and the copending claims, it is noted that the determination of the optimum dosage amounts would have been well within the purview of the skilled artisan and would have been made in accordance with a variety of factors, including, but not limited to, the age, sex, weight, diet, and medical condition of the patient, toxicological considerations and the severity of the disease. Furthermore, it is noted that while the present claims do not expressly states the other excipients or type of dosage form into which the active agents are formulated, the determination of the optimum type of formulation and the appropriate excipients or carriers to be used in such a formulation would also have been a matter well within the purview of the skilled artisan and is not seen to be inconsistent with what would have been used by the skilled artisan.

The present claims provide for the treatment of hypertension combined with hyperlipidemia or atherosclerosis, prediabetes, diabetes mellitus, metabolic syndrome or insulin resistance, which is clearly provided for in the copending claims. While the present claims do not expressly recite the use of a diuretic in combination with the claimed combination of agents, the use of such would have been *prima facie* obvious to one of ordinary skill in the art because diuretics were known as antihypertensives (see Drug Facts and Comparisons, 1996, p.632). Motivation to administer both together flows logically from the efficacy demonstrated in the prior art for individually treating the same conditions. Please see *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Accordingly, rejection of claims 1-2, 4-7 and 12-18 of the present application is deemed proper over claims 1-21 of U.S. Patent Application No. 11/300,947 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 1-18 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 24, 2006

Continuation of (3) Information Disclosure Statements: February 23, 2004 (two pages total); March 26, 2004 (one page total) and August 16, 2004 (two pages total).